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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
REDDIG, PETER J	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/728,055	MULLIGAN ET AL.	
	Examiner	Art Unit	
	PETER J. REDDIG	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,7,10,29-33,42 and 43* is/are pending in the application.

4a) Of the above claim(s) *30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,7,10,29,31-33,42 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/17/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed March 17, 2008 in response to the Office Action of September 12, 2007 is acknowledged and has been entered. Claims 1, 2, 4, 5, 7, 10, 29-33, 42 and 43 are pending. Claim 30 has been withdrawn. Claims 1 and 2 have been amended and new claim 43 has been added. Claims 1, 2, 4, 5, 7, 10, 29, 31-33, 42 and 43 are currently being examined.

2. The following rejections are being maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 2, 4, 5, 7, 10, 29, 31-33 and 42 remain rejected and new claim 43 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons set forth in section 8 and 9 of the Office Action of September 12, 2007.

5. In section 8 of the Office Action of September 12, 2007 Examiner argued:

Claim 1 and its dependent claims, claims 2, 4, 5, 7, 10, 29, 31-33 and 42, are indefinite because the term "significant expression level" in claim 1 is a relative term which renders the claim indefinite. The term "significant expression level" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. What level of significant expression is required to meet the limitations of the claims? Can the features show under expression or overexpression? Can some features be overexpressed and some under expressed? Thus, the metes and bounds of the claims cannot be determined.

Applicants point to paragraph [0041] at pages 11-12 of the specification. Applicants argue that in this paragraph, "significant" expression is defined with regard to the standard error of the assay employed to assess expression. This paragraph discusses the possibility that some features may be overexpressed (expressed at a higher level than normal) and that some features may be under expressed (expressed at a lower level than normal). This disclosure is supplemented by an overview in paragraph [0016] (page 6), which discusses controls and standards against which to judge over- and under- expression. Assay methods are provided and Applicant provides further guidance in generating results for comparing expression levels, e.g., paragraphs [0081], [0083], [0084], [00102], and [00103] provide options of deriving normalized or relative expression levels for nucleotide or antibody detection. Applicant submits that one of skill in the art of expression profiling would be familiar with statistical methods relating to the particular assay being used and would be able to recognize a level of expression that is less than or greater than the standard error of the measurement. In view of the content of the specification and the level of skill in the art, Applicant respectfully requests that this rejection be withdrawn.

Applicants' arguments have been considered, but have not been found persuasive. Although paragraph 0041 in one sentence defines significant expression with regard to standard error, paragraph 0041 gives an alternate definition in the sentence bridging pages 11 and 12 and it is not clear which definition is controlling the meaning of significant expression. Furthermore, in regard to controls, standards, normalized, or relative expression, Applicants are arguing limitation not found in the claims and the argument in this regard is also not found persuasive.

In section 9 of the Office Action of September 12, 2007 Examiner argued:

Claim 1 and its dependent claims, claims 2, 4, 5, 7, 10, 29, 31-33 and 42 are indefinite because all of the predictive markers in tables 1 and 4 are drawn to accession numbers, and no sequence listing data is found. The use of accession numbers does not satisfy the requirements of 35 USC 112, second paragraph because accession numbers and the sequences corresponding to accession numbers are not unique identifiers required for identification of mRNAs because accession numbers can be modified, changed, and/or updated, and thus the cited sequence may vary or change over time. Thus, identifying a molecule by accession number does not provide a reliable unique identifier. Amendment of tables 1 and 4 to include unique identifiers to sequences listed in a sequence listing which unambiguously define the molecules in the claimed Tables would obviate this rejection.

Applicants argue that a rejection under 35 U.S.C. § 112, second paragraph must consider whether the claims are precise and unambiguous to a reasonable degree of particularity and distinctness. The claims need to be judged on the content of the disclosure, the teachings of the prior art and the interpretation by one with ordinary skill in the art (MPEP §2173.05). A claim to a chemical compound is not indefinite merely because a structure is not presented (MPEP §2173.05(t)) and may be claimed by a name that adequately describes the material to one skilled in the art. Applicants argue that the Examiner is respectfully invited to review paragraph [0032] which defines a "marker' as "at least one of the nucleic acids or proteins associated with Affymetrix probe set identifiers" listed in the table. The Affymetrix Probe set ID numbers are provided for each of the markers in Table 1; Table 4 refers to the marker numbers identified in Table 1. The NCBI accession numbers and descriptions are provided for reasons which include 1) for convenience to aid in conceptualization of genes which typically are identified by the

probe sets; and 2) to provide the practitioner with additional sequences to devise reagents for measuring expression levels. The probe sets are a defined set of sequences compiled on each array by the manufacturer and the sequences are available to the public. Product literature provided by the manufacturer (see, e.g., the Affymetrix website technical support section) lists the sequences included in each probe set. These sequences are established under each probe set identifier by the manufacturer upon devising the array and do not change. Each probe set is composed of multiple sequences and it would be an undue burden to list all of these publicly-available sequences for every marker in the tables. For example, the sequence file provided by Affymetrix technical support for the U133A array lists eleven probe sequences for marker 149 (Probe set ID 221569_at), each about 23-26 nucleotides in length. To provide this number of sequences for every marker listed in Tables 1-3 would mean creating a sequence listing of thousands of sequences which are exact copies of what already is available to the public. Even NCBI retains and makes available dated revisions of sequences (see the "Check sequence revision history" link on the NCBI website; see Exhibits A and B for the history of marker 149 and the sequence version from March 20, 2002) so, if desired, one can retrieve a sequence in the form in which it was available as of the priority date of the present application. As described in the specification, to practice the claimed invention, one of skill in the art can use the probe sets themselves, the nucleotide sequence or polypeptide sequence in the NCBI record or any combination or portion thereof to select and devise reagents by methods known in the art and supplemented in the specification at for example at paragraphs [0087]-[00110]. One of skill in the art would recognize the probe set identifier and NCBI designation as definite guides within the means for selecting the reagents and methods to measure the expression levels.

Applicants argue that by reference to the tables which precisely identify probe set identifiers for each marker and the common designations available at the time of filing, the claims particularly point out and distinctly claim the subject matter. The information in the tables is the precise information needed to practice the claimed methods. The specification directs the skilled practitioner to the public Affymetrix information to see more about the probe set and the common designation, additional information on which, including nucleic acid and protein sequences, is publicly available at the NCBI. Thus, the tables provide the skilled practitioner with multiple avenues to choose to practice the claimed invention, either use the nucleic acid probes as published by Affymetrix, use nucleic acid probes derived from the NCBI gene entry or use polypeptide probes derived from the NCBI protein entry. Therefore, the sequences are not the essential components, but the guidance to direct the skilled practitioner publicly available sequences useful to select detection tools is the essential component. That guidance is amply provided by the claimed reference to the tables and the disclosure in the specification. In view of these remarks, Applicant respectfully requests withdrawal of the rejection.

Applicants' arguments have been considered, but have not been found persuasive. First it is noted that paragraph 0032 defines A "marker" as a naturally-occurring polymer *corresponding* (emphasis added) to at least one of the nucleic acids or proteins associated with Affymetrix probe set identifiers listed in any one of Table 1, Table 2 or Table 3, not only as "at least one of the nucleic acids or proteins associated with Affymetrix probe set identifiers". Thus, paragraph 0032 does not limit the markers to those defined by the Affymetrix probe set. Further paragraph 0032 includes, without limitation, spliced RNA which would encompass alternatively spliced forms of markers in Table 1 and 4. Thus the description of a marker in paragraph 0032 is not

sufficiently limiting to overcome the indefinite of the reference to Table 1 and 4. With regard to the Affymetrix Probe ID numbers, the claims are drawn to selecting features from the Predictive Marker and the specification teaches that "features" are gene transcripts, see 00220, and it is not clear which of version of the these gene transcripts the probes are meant to identify. Applicants point to exhibits A and B for the history of marker 149 and the sequence version from March 20, 2002 and state ". . . so, if desired, one can retrieve a sequence in the form in which it was available as of the priority date of the present application." However, a review of the Exhibits A and B shows that there are at least four versions the AL136797 are available around the priority date of the present application, and it is unclear which version one of skill in the art should refer to when using the claimed method. Further, it is noted in response to Applicants arguments, that similarly for Marker No. 1, which refers to NM_002317, there are at least ten revisions of the sequence around the priority date of the Application and it is unclear which version one of skill in the art should refer to when using the claimed method, see Appendix 1. It is noted that Section 2173.05(b) of the MPEP states that a claim may be rendered indefinite by reference to an object that is variable. Given the variable nature of the markers in Tables 1 and 4, Applicants arguments are not found persuasive and the rejection is maintained. Additionally, it is noted that Applicants' statement that "the tables provide the skilled practitioner with multiple avenues to choose to practice the claimed invention, either use the nucleic acid probes as published by Affymetrix, use nucleic acid probes derived from the NCBI gene entry or use polypeptide probes derived from the NCBI protein entry. Therefore, the sequences are not the essential components, but the guidance to direct the skilled practitioner publicly available sequences useful to select detection tools is the essential component," makes the claims reference to the tables 1 and 4 even

more ambiguous as it unclear what the features are that should be selected from Table 1 and measured as it not clear if it is the probe sequences, the Accession sequences, or something else entirely.

6. Claims 1, 2, 4, 5, 7, 10, 29, 31-33 and 42 remain rejected and new claim 43 is rejected under 35 U.S.C. 112, second paragraph, for the reasons set forth in section 12 of the Office Action of September 12, 2007.

In section 12 of the Office Action of September 12, 2007 Examiner argued:

The omitted elements in claim 1 and its dependent claims, claims 2, 4, 5, 7, 10, 29, 31-33 and 42, are: A control for comparing the expression level of the features to determine if the expression is significant or not.

Applicants argue that claims 1, 2, 4, 5, 7, 10, 29, 31-33 and 42 were considered indefinite for allegedly omitting essential elements, amounting to a gap between the elements. Applicants argue that the Examiner is of the opinion that a specific control is needed to compare the expression level of the features to determine whether the expression level is significant. In response, claim 1 is being amended to clarify the steps and antecedence within the claim. In view of this amendment, withdrawal of the rejection is respectfully requested

Applicants' arguments have been considered, but have not been found persuasive because the claims have not been amended to include a control for comparing the expression level of the features to determine if the expression is significant or not

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 2, 4, 5, 7, 10, 29, 31-33 and 42 remain rejected and new claim 43 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons set forth in sections 13-15 of the Office Action of September 12, 2007.

8. In section 13 of the Office Action of September 12, 2007 Examiner argued:

One cannot extrapolate the teachings of the specification to the enablement of the claims because the markers in Table 1 and Table 4 are only identified by accession numbers and no sequence information is given for the markers. Accession numbers and the sequences corresponding to accession numbers are not unique identifiers because accession numbers can be modified, changed, and/or updated, and thus the cited sequence may vary or change over time. Thus, undue experimentation would be required for one of skill in the art to identify and use the 475 sequences in Table 1 or the 40 sequences listed in Table 4 for the method as claimed.

Applicants argue that as discussed above, the markers in the tables are identified by the probe set identifier which refers to a set of oligonucleotide probes which do not change. What the set of oligonucleotide probes binds to is inherent in the composition of that probe set. The marker is identified by that probe set number and by providing NCBI accession numbers, the tables provide guidance to additional sequences associated with that marker. It is well within the skill in the art to retrieve the sequences from the public sources (Affymetrix and NCBI, even for the version available as of the priority date of the present application) and devise reagents to measure the expression levels by well known methods known to the art and supplemented by description, e.g., at paragraphs [0087]-[00110]. While there is work involved in practicing the

claimed method, the work does not require undue experimentation for one of skill in the art to practice the claimed method with a reasonable expectation of success.

Applicants' arguments have been considered, but have not been found persuasive. For the reasons forth above in section 5, Table 1 and 4 do not clearly identify what particular sequences or gene transcripts correspond to the features listed in Table 1 and Table 4 and which ones are to be use in the claimed method. Thus, one of skill in the art cannot predictable make and use the claim invention without being able to determine which sequences in particular are encompassed by Tables 1 and 4. Additionally, it is noted that nothing in paragraphs [0087]-[00110] point to which sequences or gene transcripts Table 1 and 4 are referring.

9. In section 14 of the Office Action of September 12, 2007 Examiner argued:

One of skill in the art cannot extrapolate the teachings of the specification to the enablement of the claims because **NO** nexus has been established between determining the level of expression off the features in the predictive marker set of Table 4 and determining a bortezomib regiment for treating myeloma and because those of ordinary skill in the art recognize that identification of prognostic markers is unpredictable.

In particular, Mulligan et al. (Blood, 2007. 109:3177-3188, IDS) teach that although they identified a pretreatment pattern of pretreatment gene expression pattern and predictive classifier that is significantly associated with subsequent myeloma response to bortezomib but not dexamethasone, the predictive accuracy required of a clinical diagnostic for myeloma treatment has not yet been defined, see p. 3186, 4th full para. and last para. Furthermore, Mulligan et al. teach that the "Requirements may vary according to disease stage, therapeutic options, (single agent versus combination regiment) and whether therapy is likely to achieve disease control or

cure. Although the classifier described here is promising, further refinement is necessary before it can be considered for clinical used in predicting patient response to single –agent bortezomib in the relapsed setting . . . Additional research is needed to assess the relevance of these genomic predictors in newly diagnosed myeloma . . . " see p. 3186, last para. Given the above and given that the predictive marker set of Table 4 is not the maker set for myeloma identified by Mulligan et al., in the absence of additional, undue experimentation, one of skill in the art could not determine a bortezomib regimen for treating myeloma based on the level of expression of the features in the predictive marker set of Table 4.

Furthermore, although drawn to prognostic markers for early lung cancer detection, the basic principles taught are clearly applicable to determining a bortezomib regimen for treating myeloma based on the level of expression of the features in the predictive marker set of Table 4. Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a prognostic biomarker to successful clinical application. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early markers of carcinogenesis that have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (p. 2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known cancer outcome. The essential element of the validation of a marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of cancer and link those marker results with subsequent histological confirmation of disease. This

irrefutable link between marker and subsequent acknowledged disease is the essence of a valid marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of determining a bortezomib regimen for treating myeloma based on the level of expression of the features in the predictive marker set of Table 4, the predictive marker set must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2).

Applicants argue that the Examiner cited a publication by Mulligan et al. in which additional work was discussed. Applicant respectfully traverses this rejection. This statement was made in the context of noting that the studies described in the publication (and in the present patent application) used samples from patients who had relapsing and refractory multiple myeloma. The comment noted that another set of samples from newly diagnosed patients might be worth studying for confirming the results where previous treatment could not possibly be contributing to the results. Another aspect of this comment is that in the studies, the patients were treated with single agents, while frequently, they are treated with a combination of agents. So samples from such patients would be desired to confirm the results of the present studies. Applicant notes that since this study, the work determining markers to aid in therapy and diagnosis has continued. Submitted herewith in a supplemental IDS is a publication (Agnelli et al. 2005) wherein the authors used probe sets from the Affymetrix arrays to study the expression of three markers in samples from newly diagnosed patients. One of these markers, CCND2, marker no. 841 in the present application, was confirmed to play a role in one of the multiple myeloma tumor subtypes.

Applicants' arguments have been considered, but have not been found persuasive because the teaching of Agnelli et al. are not drawn to determining a bortezomib therapy regimen by using predictive marker sets selected from Table 1 and thus are not probative as to the enablement of the claimed invention. Additionally, whether or not marker no. 841 plays a role in multiple myeloma tumor subtypes does not support for it being a maker for bortezomib therapy and it provides no indication as to whether or not the claimed method can be used for determining a bortezomib therapy regimen.

Applicants argue that the Examiner introduced the Tockman et al. publication to illustrate the allegedly large amount of research needed to validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence and confirm marker predictive value in prospective population trials. The Examiner alleged that little is known in the prior art about the nature of the invention in this allegedly unpredictable art and that the specification provided insufficient guidance for enabling one to practice the invention. Applicants argue that the Tockman et al. article was published in 1992, ten years before the priority date of the present application and well before many of the advances in biochemistry and molecular biology from which the present studies benefit. For example, the human genome was sequenced during the intervening time and many advanced detection and quantification methods were developed and many additional reagents became available. One note regarding the Agnelli et al. reference is that it evidences the public availability of gene expression data for multiple myeloma (see page 7297 and reference 16 cited therein (Zhan et al, March, 2002). So the skilled practitioner by the priority date of this application even had data with which to compare expression results obtained when practicing the claimed invention. Second, the

Tockman et al. article is focused on methods for early detection and diagnosis of tumor using samples from sputum which may not necessarily comprise tumor cells. The present claims focus on confirmed tumor samples. Third, it is understandable that Tockman et al article would state that a prospective clinical study would be needed to confirm their results because of their focus on detection of lung cancer in asymptomatic individuals. However the studies in the present application are performed on clinical specimens. The prospective clinical specimens are inherent to the working examples disclosed in the present specification. The focus of the present application is not whether the individuals have cancer, but whether the markers can predict whether a treatment is suitable for the patients. The outcome of the clinical trial was taken into account when the markers were classified as responsive or non-predictive.

Applicants' arguments have been considered, but not found persuasive. Although the Tockman reference is old, the requirements for validation of a biomarker remain valid. Although the art has progressed from the time that Tockman et al. was published, the sequencing of the human genes and advances in detection and quantification of gene products, do not obviate the need for biomarker validation. Additionally, the presence of multiple myeloma expression data in the art does not enable the selection of predictive markers and predictive marker sets for determining a bortezomib therapy because the general expression data provides no empirical evidence that the expression levels of the genes can be used to indicate responsiveness to bortezomib. Thus the cited references are not probative on the enablement of the claimed invention. Although the markers were identified using clinical samples, the samples were not prospective clinical specimens as the specimens were from treated patients and there is no validation that markers can be used to predict whether a bortezomib therapy treatment is suitable

for the patients. The identification of markers that change expression in response to bortezomib therapy does not provide the art recognized validation of predictive biomarkers as set forth in Tockman et al.

10. In section 15 of the Office Action of September 12, 2007 Examiner argued:

One cannot extrapolate the teachings of the specification to the enablement of the claims because no nexus has been established between any expression level of the markers in Table 4 and any indication that a patient is responsive or non-responsive to bortezomib therapy. The specification has not taught the use of the marker set of table 4 for determining a bortezomib therapy regimen for any patient. There is no teaching as to what levels of expression of the markers in Table 4 will be significant for indicating responsiveness or nonresponiveness. There is no teaching as to whether the marker set of Table 4 can be used for indicating responsiveness, non-responsiveness, or both. There is no teaching if just some or all of the markers in Table 4 are needed to determine a bortezomib therapy regimen. Thus, given the above, undue experimentation would be required for one of skill in the art to make and use the invention as claimed.

Applicants argue that the response for Paragraph 10 on previous page 11 explained how to use Table 4 to determine whether a new multiple myeloma patient will be sensitive or resistant to bortezomib therapy. Briefly, paragraph [00236] teaches that the vote weights obtained after using the weight and decision boundary and the expression level of each Table 4 marker in the sample are added to obtain a sum which determines responsiveness or nonresponsiveness of the patient's tumor. An example of applying the weighted voting method was used in the example providing Table 5 (paragraph [00249]). In that example, the patient was predicted to be non-

responsive when the five vote weights were added. Applicant submits that the usage of this method is enabling from the teachings in the specification and the content of Table 4. The only thing the skilled practitioner would have to do besides the vote weight calculations is determine the expression level of the markers in Table 4. The methods for determining expression, e.g., mRNA detection, are well known in the art and are supplemented in the application, e.g., at paragraphs [0087]-[00101] and further supplemented by the working example beginning at paragraph [00199]. In view of these remarks, withdrawal of this rejection is respectfully requested.

Applicants' arguments have been considered, but have not been found persuasive because Applicants are arguing limitations not found in the claims. In particular the claims are not drawn to obtaining vote weights using the weight and decision boundary and the expression level of each Table 4 marker or using the weighted voting method. Additionally, although the methods of determining RNA expression are well known in the art, the claims are not limited, and for the reasons set forth above and previously, the rejection are maintained.

11. Claims 1, 2, 4, 5, 7, 10, 29, 31-33 and 42 remain rejected and new claim 43 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons set forth in section 16 of the Office Action of September 12, 2007.

In section 16 of the Office Action of September 12, 2007 Examiner argued:

The claims are broadly drawn to a method for determining a bortezomib therapy regimen for treating a myeloma in a patient comprising: a) selecting features from the Predictive Markers in Table 1, to select a predictive marker set; b) determining the level of expression of the features in the predictive marker set; and c) determining a bortezomib regimen for treating the tumor

based on the expression of the features in the predictive marker set, wherein a significant expression level is indicative that the patient is either a responsive patient or a non-responsive patient, wherein the expression level is determined by mRNA detection.

The state of the art is such that it is well know in the art that identification of biomarkers is unpredictable. In particular, In particular, Mulligan et al. (Blood, 2007. 109:3177-3188, IDS) teach that although they identified a pretreatment pattern of pretreatment gene expression pattern and predictive classifier that is significantly associated with subsequent myeloma response to bortezomib but not dexamethasone, the predictive accuracy required of a clinical diagnostic for myeloma treatment has not yet been defined, see p. 3186, 4th full para. and last para. Furthermore, Mulligan et al. teach that the "Requirements may vary according to disease stage, therapeutic options, (single agent versus combination regiment) and whether therapy is likely to achieve disease control or cure. Although the classifier described here is promising, further refinement is necessary before it can be considered for clinical used in predicting patient response to single –agent bortezomib in the relapsed setting . . . Additional research is needed to assess the relevance of these genomic predictors in newly diagnosed myeloma . . . " see p. 3186, last para. Furthermore, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a prognostic biomarker to successful clinical application. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Early markers of carcinogenesis that have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (p.

2713s, col 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known cancer outcome. The essential element of the validation of a marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of cancer and link those marker results with subsequent histological confirmation of disease. This irrefutable link between marker and subsequent acknowledged disease is the essence of a valid marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points).

Given the above and given that Table 1 has 171 features with a signal to noise ratio method rank of under 100 from which to chose to select a predictive marker set, which is approximately 1.2×10^{309} combinations by factorial analysis (that is $171! = 7.5 \times 10^{309}$), However, the specification provides no written description of which set will in fact function as claimed. An adequate written description of the predictive marker set that is useful for determining a bortezomib therapy regimen is required for one of skill in the art to use the claimed invention.

Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name,' of the

claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such

characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The inventions at issue in Lilly and Enzo were DNA constructs per se, the holdings of those cases are also applicable to claims such as those at issue here. A disclosure that does not adequately describe a product itself logically cannot adequately describe a method of using that product.

Thus, the instant specification may provide an adequate written description of a predictive marker set that is useful for determining a bortezomib therapy regimen, per Lilly by structurally describing a representative number of predictive marker sets that are useful for determining a bortezomib therapy regimen, or by describing "structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per Enzo, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

In this case, the specification does not describe a predictive marker set that will function as claimed, that is useful for determining a bortezomib therapy regimen, in a manner that satisfies either the Lilly or Enzo standards. The specification does not provide the complete structure of any predictive marker set that is useful for determining a bortezomib therapy regimen, nor does the specification provide any partial structure of such a predictive marker set that is useful for determining a bortezomib therapy regimen, nor any physical or chemical characteristics of a predictive marker set that is useful for determining a bortezomib therapy

regimen, nor any functional characteristics coupled with a known or disclosed correlation between structure and function. Although the specification discloses Table 4, 5, and 6, there is no teaching that these sets will in fact function as claimed and even if they were to function as claimed, this does not provide a description of a predictive marker set that is useful for determining a bortezomib therapy regimen that would satisfy the standard set out in Enzo especially given that the number of sets claimed exceeds the numbers of stars in the known universe.

The specification also fails to describe a predictive marker set that is useful for determining a bortezomib therapy regimen by the test set out in Lilly. The specification describes only Tables 4, 5, and 6, but there is no teaching that these sets will in fact function as claimed and even if they were to function as claimed, given that the number of sets claimed exceeds the numbers of stars in the known universe, the sets described in the three tables do not meet the test set out in Lilly. Therefore, it necessarily fails to describe a "representative number" of a predictive marker set that is useful for determining a bortezomib therapy regimen. In addition, the specification also does not describe "structural features common to the members of the genus, which features constitute a substantial portion of the genus."

Thus, the specification does not provide an adequate written description of a broadly claimed predictive marker set that is useful for determining a bortezomib therapy regimen that is required to practice the claimed invention or reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the broadly claimed invention. Since the specification fails to adequately describe or reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had

possession of the broadly claimed predictive marker set that is useful for determining a bortezomib therapy regimen, it also fails to adequately describe the claimed method or reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argue that the specification also provides Tables 2, 3, 7 and 8, which describe additional species of markers. Tables 2 and 3 provide species which are associated with time to progression or progressive disease and Tables 7 and 8 are disclose markers associated with biological annotations or tumor cell lines. As discussed above, the identification of the markers in the tables is sufficient for one of skill in the art to recognize the structures associated with the claimed methods. By the working examples represent markers identified in a clinical setting and Table 1 identifies markers as being associated with responsiveness or non-responsiveness. At the time of filing, one of skill in the art would recognize the genus of methods claimed in claim 1, using the markers in Table 1, of which Tables 1, 4, 5, 6, 7, and 8 are included as method species is adequately described. As discussed above, the specification does provide the structures recognizable and retrievable to one of skill in the art and methods are described to utilize the structures. In view of these remarks, withdrawal of the rejection is respectfully requested.

Applicants' arguments have been considered, but have not been found persuasive. First, Table 2, 3, 7, and 8 are not predictive marker sets for determining a bortezomib therapy regimen as Table 2 is characterized as being a table of markers for time until disease progress in patients with relapsed and refractory multiple myeloma after bortezomib, the markers in Table 3 appear to be distinct from those in Table 1, so are not pertinent to a predictive marker set selected from Table 1, Table 7 is simply a biological annotation of the markers , and Table 8 is drawn to genes

present in resistant or sensitive cell lines. Although Tables 4-6 are characterized as predictive marker sets selected from Table 1, given the broadly claimed predictive marker sets claimed (1.2×10^{309} combinations) the markers set forth in Tables 4-6 do not adequately describe the broadly claimed predictive marker set.

12. Claim 42 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons set forth in section 18 of the Office Action of September 12, 2007.

In section 18 of the Office Action of September 12, 2007 Examiner argued:

Claim 42 is rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of "a predictive marker set comprises Predictive Marker No. 149" claimed in claim 42 has no clear support in the specification and the claims as originally filed. A review of the specification and claims as originally filed has not identified support for the newly filed claim and Applicant has not specifically pointed to support for this newly filed claim. The subject matter claimed in claim 42 broadens the scope of the invention as originally disclosed in the specification.

Applicants argue for support of claim 42 in paragraph 0017.

Applicants' arguments have been considered, but have not been found persuasive. A review of paragraph 0017 reveals support for:

> Methods of the invention can use at least one of the predictive markers set forth in any one of Table 1, Table 2, Table 3, Table 4, Table 5, Table 6, or Table 7. Additionally, the methods provided can use two, three, four, five, six, or more markers to form a predictive marker set. For example, marker sets selected from the markers in Table 1, Table 2 and/or Table 3 can be generated using the methods provided herein and can comprise between two, and all of the markers set forth in Table 1, Table 2 or Table 3 and each and every combination in between (e.g., four selected markers, 16 selected markers, 74

selected markers, etc.). In one embodiment, the markers comprise those set forth in Table 4, Table 5 or Table 6.

The cited support is not found persuasive because there is nothing to provide support for the newly claimed genus of predictive marker sets comprising Predictive Marker NO. 149. Thus, the rejection is maintained.

New Grounds of Rejection/Objection

Specification

13. The disclosure is objected to because of the following informalities: The amendment to the specification filed March 17, 2008 replaces paragraph 0041 with a paragraph 00158. Although the paragraph appears to be the same as the original paragraph 0041, with the indicated changers, the paragraph should be numbered 0041 to keep the correct numbering.

Appropriate correction is required.

14. All other objections and rejections recited in the Office Action of September 12, 2007 are withdrawn.

15. No claims allowed.

16. This action is a **final rejection** and is intended to close the prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an appeal to the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below.

If applicant should desire to appeal any rejection made by the examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims appealed. The Notice of Appeal must be accompanied by the required appeal fee.

If applicant should desire to file an amendment, entry of a proposed amendment after final rejection cannot be made as a matter of right unless it merely cancels claims or complies with a formal requirement made earlier. Amendments touching the merits of the application which otherwise might not be proper may be admitted upon a showing a good and sufficient reasons why they are necessary and why they were not presented earlier.

A reply under 37 CFR 1.113 to a final rejection must include the appeal form, or cancellation of, each rejected claim. The filing of an amendment after final rejection, whether or not it is entered, does not stop the running of the statutory period for reply to the final rejection unless the examiner holds the claims to be in condition for allowance. Accordingly, if a Notice of Appeal has not been filed properly within the period for reply, or any extension of this period obtained under either 37 CFR 1.136(a) or (b), the application will become abandoned.

17. Applicant's amendment necessitated the new grounds of rejection. Thus, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter J. Reddig whose telephone number is (571) 272-9031. The examiner can normally be reached on M-F 8:30 a.m.-5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Peter J Reddig/

Examiner, Art Unit 1642

/P. J. R./

/Karen A Canella/

Primary Examiner, Art Unit 1643